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Epidemiology and outcomes of Group A streptococcal and non-Group A streptococcal septic arthritis in French children between 2010 and 2023, a national cohort analysis, and case-control study

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ABSTRACT

Background: Invasive Group A streptococcal (GAS) infections in children are rising across Europe, yet GAS as a cause of septic arthritis (SA) remains poorly characterized. We aimed to describe the incidence trajectory of GAS SA in France, its clinical presentation relative to non-GAS SA, and predictors of sequelae.

Methods: A retrospective national multicenter cohort study with nested case-control elements in children aged 3 months to 16 years was undertaken. Cases were culture- or PCR-confirmed GAS SA from 15 tertiary pediatric orthopaedic centres in France; controls were non-GAS SA patients. Crude and age-standardized incidence rates were calculated for the period 2010–2023. Multivariable logistic regression with cluster-robust standard errors identified predictors of GAS aetiology and of functional sequelae at 30-day follow-up.

Findings: 137 GAS SA cases and 321 controls were included. GAS SA incidence rose steadily from 2010 onwards. The crude national incidence rate for 2021–2023 was 0.311 per 100,000 children under 15 years (95% CI 0.24–0.39), approximately 34 cases annually. GAS aetiology was independently associated with age 2–8 years, antalgic joint positioning (OR 3.94, 95% CI 1.61–9.67), elevated CRP (OR 1.14 per 10 mg/L, 95% CI 1.09–1.18), and concurrent skin or soft tissue infection, (OR 4.68, 95% CI 1.29–16.98, p=0.02). Presenting with a SA in a large joint decreases the risk of GAS being the causative organism (OR 0.50, 95% CI 0.26–0.94, p=0.03). Sequelae occurred in 24.8% of GAS SA, comparable to S. aureus SA (41.7%). Predictors of sequelae included longer symptom duration (OR 1.08 per day, 95% CI 1.03–1.12), concurrent osteomyelitis (OR 4.47, 95% CI 2.16–9.27), reintervention (OR 3.64, 95% CI 1.79–7.42), concurrent skin infection (OR 3.80, 95% CI 1.46–9.88), and pre-hospital antibiotics (OR 2.37, 95% CI 1.29–4.33).

Interpretation: GAS SA is an emerging paediatric pathogen with a distinct clinical profile and sequelae burden comparable to S. aureus SA. Delayed treatment is a key modifiable predictor of poor outcomes; early recognition by orthopaedic surgeons, paediatricians, and primary care providers is essential.

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Introduction

Group A streptococcus (GAS) infections, including rare osteo-articular infections, have been on the rise in Europe, and in France since the early 2000s without a clear cause [1–3]. GAS is a common causative organism of childhood infections such as pharyngitis and scarlet fever [1,4,5]. However, it can also cause more invasive infections (iGAS) such as necrotizing fasciitis or meningitis, with European mortality rates reported to be 3.6–5% [1,4–7]. An estimated 3–5 per 100.000 GAS infections is associated with invasive osteoarticular infections [5]. Despite still being rare, larger academic centers now see several cases annually [8], prompting the need to explore its clinical presentation and outcomes.

Septic arthritis (SA) is a distinct subtype of osteoarticular infections, which presents as an infection of a joint cavity either through direct inoculation, hematogenous spread from another site of infection or secondary to an adjacent osteomyelitis [9–11]. Compared to non-SA musculoskeletal infections, SA often requires surgical expertise during the diagnostic or treatment phase [9–13], making it critical to understand the clinical signs of a potential SA to prompt a timely, multidisciplinary diagnostic work-up and treatment plan. If not treated rapidly, SA can lead to life-long disability due to cartilage degeneration or physeal closure leading to limb length discrepancies, and in extreme cases to disseminated infections and death. [10,12,13]

In Europe, currently, two organisms dominate the pediatric SA microbiology: *Kingella Kingae* is the most common causative organism in children under 4 years of age, and *Staphylococcus aureus* is the most common organism in children above age 4 years; while GAS infections remain in the single digits, and 20% of pediatric SA cases remain without an identifiable causative organism despite improved detection methods [14]. Clinically, K. Kingae SA is known for its indolent clinical presentation, and sometimes self-limiting disease, while S. Aureus and GAS SA are aggressive pathogens with a risk of evolving into a severe multi-organ invasive infection with increased morbidity and mortality [8,15,16]. These known differences in clinical presentation re-emphasize that pediatric SA is not a clinical monolith, and a better understanding of the differences in clinical presentation and outcomes, can support the development of germ-based diversified treatment protocols.

Most pediatric osteo-articular infection studies focus on SA and osteomyelitis combined, with osteomyelitis being the more common clinical presentation and often dominating the results [9,17]. Consequently, there is a lack of literature focusing specifically on pediatric SA symptomatology and outcomes [9], and even less literature devoted to pediatric osteoarticular GAS infections [8,15]. This exploratory national retrospective epidemiological study aims to describe the clinical presentation of pediatric GAS SA in contrast to non-GAS SA, and their differences in clinical outcomes. Additionally, we assess the evolution of GAS SA incidence across France.

Methods

Study design and setting

This study is a retrospective, multi-center, national cohort study with nested case-control elements to explore the clinical presentation of the GAS SA and identify clinical variables associated with sequelae. As GAS SA is a rare disease, cases were sourced from multiple hospitals with complete case ascertainment to increase the power and sample size of our study. Controls were sourced from a single Parisian tertiary pediatric hospital treating 50–100 cases of osteoarticular infections annually, as the collection of multi-center controls was unfeasible. We were unable to find any study exploring or describing the differences in the SA patient population between hospitals in the same region or health care system. As an internal validation for the assumption that the Necker hospital SA patient population is equal in demographic and clinical presentation to the patient populations elsewhere in France, we compared the GAS patient population from Necker to the GAS patient population in the rest of Paris and the rest of the country (Table S1). The Necker GAS SA population was more affluent and sicker, if this trend is equally present in the non-GAS SA population across France, we may underestimate the proportion of ORs in the multivariable models. Department chairs of all 26 tertiary-level pediatric orthopaedic surgery departments in mainland France were invited by email in the spring of 2023 to participate in this study.

Participants

The inclusion criteria communicated to participating hospitals were wider than the inclusion criteria applied in the actual study. This allowed a more reproducible and robust process of patient screening for inclusion. Data was requested from participating hospitals for all types of GAS osteoarticular infections in patients between 0 and 18 years treated within the inclusion period. All patients with a GAS SA requiring an irrigation and debridement procedure in the operating room, and a joint aspirate culture or PCR positive for GAS were considered for inclusion in this study. The inclusion period ran from 1/1/2010 to 31/12/2023 for GAS SA and 1/1/2016 to 31/12/2023 for non-GAS SA due to limited availability of non-GAS SA data prior to 2016. Patients with a microbiology specimen positive for an undefined type of streptococcus were excluded. Non-GAS SA controls were drawn from an institutional database on community-acquired pediatric osteoarticular infections at the Necker Children's Hospital in Paris, France (supplement p8). Patients from the database were eligible for inclusion if the causative pathogen was not GAS and if their SA was an SA according to the international guidelines [18]: they received an irrigation and debridement in the operating room, and a causative pathogen was identified on the joint aspirate or the joint aspirate was turbid or purulent but remained culture-negative. The age cut-offs were set at 3 months to 16 years in the control group to avoid including SA due intrapartum infections and because children older than 16 years can generally no longer be hospitalized at Necker. The same age cut-offs were applied to the cases, to create two comparable cohorts.

In order to obtain a sample representative of the general healthy pediatric population we excluded patients with sickle cell anemia, an immunosuppressed state, a diagnosed rheumatologic disease, an SA diagnosed after surgery to the respective joint or due to direct inoculation or trauma, and patients with a soft-tissue infection without clear involvement of a joint or infection of a non-synovial joint.

Variables

Baseline demographic data, pre-operative clinical presentation and symptomatology, peri-operative microbiological, laboratory, radiological and surgical treatment data, and data on the post-operative outcomes up to three months post-treatment were extracted from patient files for cases and controls. For GAS infections emm-typing was extracted from patient files if typing is performed as a standard procedure at the treating institution. The affected joint was recategorized as large or small, with hip, knee and shoulder counting as large, and all other joints as small.

Expected poverty and rurality rates for the Necker and national catchment areas were calculated based on publicly available data from the Institut National de la Statistique et des Etudes Economiques (supplement p6).

A reintervention was limited to a repeat irrigation and debridement to control the infection, and did not include any surgeries required to address potential sequelae later in the disease course. Sequelae were defined as any structural lesion with long-term functional implications caused by the SA and diagnosed at 30 days or more post-operatively. Sequelae were subcategorized as: osteolytic lesion, epiphysiodesis, persistent stiffness, and complete soft tissue destruction.

Table 1
Baseline demographics of GAS and non-GAS SA patients.

	Non-GAS Septic arthritis (n = 321)			GAS Septic arthritis
	Total (n = 321)	K. Kingella SA (n = 176)	S. Aureus SA (n = 28)	GAS SA (n = 137)
Basic demographics				
Age at time of admission (months), median (IQR)	18.0 (12.0-44.0) (321/321)	14.0 (10.0-19.0) (176/176)	115.5 (67.8-142.5) (28/28)	47.0 (18.0-82.0) (137/137)
Male, n (%)	183/321 (57.0)	100/176 (56.8)	20/28 (71.4)	68/136 (50.7)
Female, n (%)	138/321 (43.0)	76/176 (43.2)	8/28 (28.6)	68/136 (49.3)
Household poverty rate, mean±SD	12.6±6.2 (319/321) (Expected 13.4%)	12.1±5.4 (176/176)	13.2±7.3 (27/28)	17.6±7.6 (133/133) (Expected 14.1)
Living in rural area, n (%)	12/319 (3.8) (Expected 6%)	4/176 (2.2)	3/27 (11.1)	21/133 (15.8) (Expected 33%)
Important past medical history, n (%)	6/321 (1.9)	2/176 (1.1)	0/28 (0)	8/128 (6.2)
Concomitant infections				
Ear/nose/throat total, n (%)	78/320 (24.4)	47/175 (26.9)	1/28 (3.6)	37/100 (37.0)
Gastro-intestinal, n (%)	15/320 (4.7)	7/175 (4.0)	2/28 (7.1)	15/100 (15.0)
Pulmonary, n (%)	22/320 (6.9)	18/175 (10.3)	0/28 (0)	7/100 (7.0)
Urogenital, n (%)	2/320 (0.6)	1/175 (0.6)	0/28 (0)	3/100 (3.0)
Skin/soft tissues infection, n (%)	10/320 (3.1)	2/175 (1.1)	1/28 (3.6)	37/112 (33.0)
Other, n (%)	1/320 (0.3)	0/175 (0)	0/28 (0)	0/100 (0)
Any predisposing infection, n (%)	106/320 (33.1)	61/175 (34.9)	4/28 (14.3)	76/112 (67.9)
Other predisposing events				
Closed trauma to affected joint, n (%)	7/320 (2.2)	2/175 (1.1)	1/28 (3.6)	2/100 (2.0)
Recent surgical interventions (last 14 days), n (%)	0/320 (0)	0/175 (0)	0/28 (0)	5/100 (5.0)

Number of patients included per variable differs based on availability of data for that specific variable

Bias

The risk of double-counting patients was kept to a minimum by excluding patients who received their surgical intervention at another institution. Departments were contacted for clarifications if patient data contained outliers compared to the rest of the dataset.

Statistical analysis

Baseline data for cases and controls are presented as mean and standard deviation (SD) for normally distributed continuous data, median and interquartile range (IQR) for non-normally distributed continuous data, and number and percentage for dichotomous and categorical variables. Baseline data were explored for GAS SA, all non-GAS SA, K. kingae SA, and S. aureus SA.

After visual assessment of missingness patterns (Fig. S2-S3), data were assumed to be missing at random (MAR) or missing completely at random (MCAR) (supplement p11). Missing data were imputed using multiple imputation with chained equations (mice package in R) with 10 imputations. Results were pooled across imputations using Rubin's rules.

Baseline clinical variables for inclusion in the multivariable models were identified based on clinical relevance and existing literature (supplement p10). Additional variables for inclusion were identified using a Directed Acyclic Graph (supplement p9) that was developed before the start of the study (Fig. S1). In order to maintain an events-per-variable (EPV) ratio of 8–10 in the multivariable analyses, only significant additional variables based on exploratory univariable logistic regression analyses including additional clinical variables, and interaction terms for age and affected joint (Table S7-S8), were considered for inclusion. Significance of interaction terms was assessed using the Wald test. Factor-level odds ratios (ORs) were calculated for significant variables or interactions only. Variables known at the time of admission were considered for inclusion in both multivariable models, while variables known in the early post-operative period were only considered in the sequelae model. Model performance was assessed using the C-statistic (area under the receiver operating characteristic curve), McFadden's Pseudo R^2, Hosmer-Lemeshow test, and variance inflation factors (VIF) to evaluate discrimination, model fit, calibration, and multicollinearity, respectively.

For the analysis identifying clinical variables significantly associated with GAS versus non-GAS SA, all cases and controls were retained. The nested case-control analysis of variables associated with sequelae after SA was performed including only cases and controls with minimum 30-day follow-up data. To assess for selection bias, baseline characteristics and clinical variables were compared between patients with and without documented follow-up (Table S2) (supplement p12). To account for clustering of patients within participating hospitals, standard errors were adjusted using cluster-robust variance estimation (sandwich estimator).

Regional and national crude and age-standardized incidences of GAS SA were calculated for the periods 2010–2013, 2014–2017, 2018–2020, 2021–2023. The European (EU-27 plus EFTA 2011–2030) standard population was used for age-standardization [19]. For hospitals with missing data during a specific year, the weighted mean for that year and age group based on available data from other centers was imputed. The denominators for the incidence rate calculations were determined using the publicly available population numbers from the INSEE for each hospital catchment area as determined by the French government (supplement p7). A p-value <0.05 was considered statistically significant. All statistical analyses were performed using RStudio version 2025.05.1+513 (RStudio Team, RStudio, Boston, MA, USA).

Ethics statement

Ethical clearance for a national retrospective multi-center study was obtained from the "Comité de Protection des Personnes Sud Méditerranée I" with registration number #00011928.

Supplementary methods section

An overview of the French health care system (supplement p3), and a complete overview of included variables and their operational definitions (supplement p3), can be found in the supplement.

Role of the funding source

There was no funding for this study

Table 2
Age-adjusted incidence rates per 100,000 children with exact Poisson 95% confidence intervals.

	0-4 years	5-9 years	10-14 years	Total cohort
2010-2013	0.083 (0.028 – 0.190)	0.016 (0.000 – 0.091)	0.034 (0.004 – 0.123)	0.045 (0.020 – 0.088)
2014-2017	0.262 (0.162 –0.401)	0.104 (0.046 – 0.202)	0.055 (0.016 – 0.136)	0.140 (0.097 – 0.196)
2018-2020	0.347 (0.215 – 0.529)	0.082 (0.028 – 0.186)	0.048 (0.011 – 0.137)	0.154 (0.104 – 0.220)
2021-2023	0.607 (0.434 – 0.826)	0.299 (0.188 – 0.453)	0.051 (0.014 – 0.132)	0.304 (0.235 – 0.387)

Results

A total of 137 cases (Fig. S4-S5, Table S3), out of 199 reviewed patient files from 15 hospitals; and 321 controls (Fig. S6), out of 1394 reviewed patients, were included in this study. Age demographics differed significantly between SA causative organisms (Table 1), with K. kingae patients having a median age of 14.0 months (IQR 10.0–19.0), S. aureus patients 115.5 months (IQR 67.8–142.5), and GAS patients 47.0 months (IQR 18.0–82.0). K. kingae-infected patients had high rates of concurrent ENT (26.9%) and pulmonary infections (10.3%), while GAS-infected patients had substantially higher rates of ENT (37.0%) and skin/soft tissue infections (33.0%), of which 81% (30/37) constituted varicella infections (Table S4).

Compared with national estimates, GAS cases had a higher-than-expected poverty rate (17.6% vs 14.1% expected) and lower-than-expected rurality rate (15.8% vs 33% expected), while non-GAS patients only had a minimally lower-than-expected poverty (12.6% vs 13.4% expected) and rurality rate (3.8% vs 6% expected (Table 1). Living in an urban area was significantly associated with a loss-to-follow-up after 30 days for GAS patients (31.3% vs 4.8%, p=0.014) (Table S2). Among GAS-patients with follow-up, living in a rural area was associated with a decreased risk of developing a sequela (OR 0.67, 95% CI 0.20–2.23, p=0.5802), however the association did not reach significance (Table S9).

The age-adjusted national incidence rate of GAS SA has been increasing steadily since 2010 in both the 0–4-years and 5–9-years age groups and have remained stable in children between 10–14 years (Table 2, Fig. 1). The increase in incidence slowed between 2018–2020 but accelerated again in 2021–2023. For the period 2021–2023, the crude national incidence rate of GAS SA in children was determined to be 0.311/100,000 children (95% CI 0.235 – 0.387/100,000) aged 0–14.9 years old. With an estimated 11 million children under the age of 15 years in France [20], this translates to about 34 (95% CI 26–43) cases annually. An overview of age-adjusted incidence rates in earlier periods and per age category can be found in Table 2.

GAS patients were sicker at initial presentation compared to non-GAS patients (Table 3), with higher median temperature (38.9°C [IQR 38.1–39.3] vs 38.2°C [IQR 37.3–38.7]), CRP (107.5 mg/L [IQR 56.7–204.2] vs 40.0 mg/L [IQR 18.0–61.0]), and leucocyte count (17,500 cells/μL [IQR 11,300–22,600] vs 12,120 cells/μL [IQR 9550–15,300]). GAS patients presented more often with antalgic positioning (60.9% vs 29.2%) and stiffness of the affected joint (78.6% vs 61.2%). GAS patients had lower rates of preoperative osteolysis (28.3%) compared to S. aureus patients (30.8%). GAS and S. aureus patients had similar reintervention rates (35.8% vs 32.1%); however, S. aureus patients had higher rates of complicated arthritis (42.8% vs 13.1%) and sequelae (41.7% vs 24.8%). Among the non-GAS patients, 70.7% of patients had a germ identified through microbiologic testing (Table S5). Patients with an S. aureus infection or GAS infection received longer intravenous and oral antibiotic treatment compared to non-S. aureus/non-GAS patients (Table S6).

The first multivariable risk model (Fig. 2, Table 4) shows that in children presenting with radiologically- or laboratory-proven SA, the following variables independently increase the risk of GAS being the

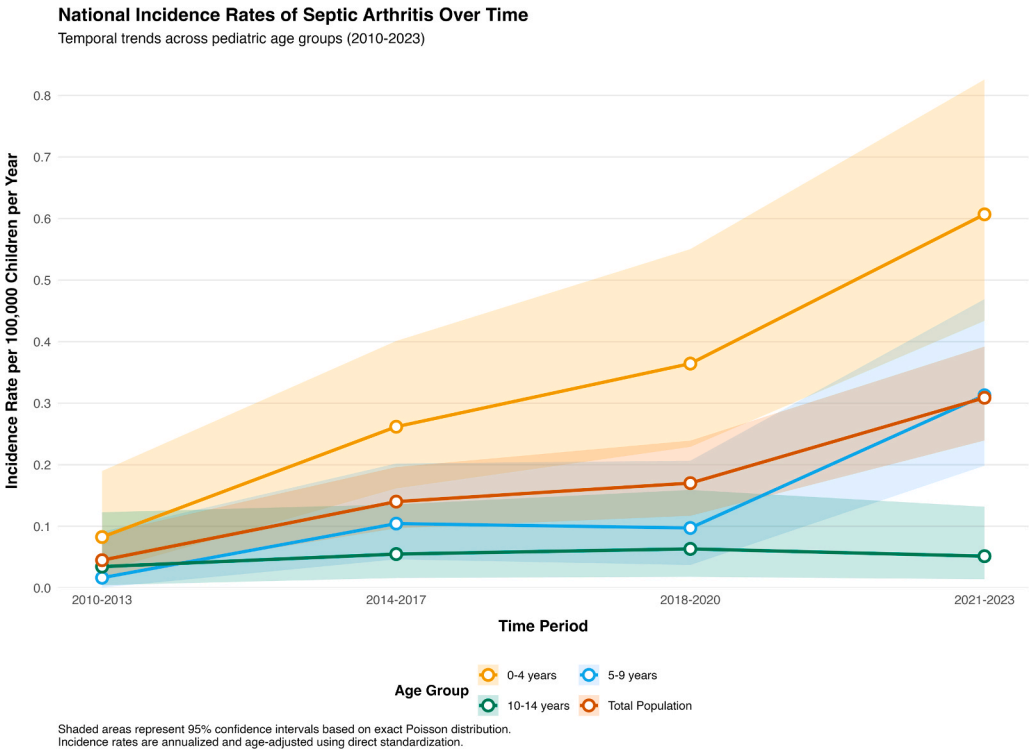

Fig. 1. National incidence rates of GAS septic arthritis over time.

Table 3
Clinical presentation and outcomes of septic arthritis.

	Non-GAS SA (n = 321)	K. Kingae SA (n = 176)	S. Aureus SA (n = 28)	GAS SA (n = 137)
Clinical presentation at time of admission				
Clinical symptoms				
Temperature (°C), median (IQR)	38.2 (37.3-38.7) (273/321)	38.2 (37.8-38.7) (149/176)	38.5 (38.0-39.0) (23/28)	38.9 (38.1 – 39.3) (132/137)
Limp/impairment, n (%)	266/312 (85.2)	154/170 (90.6)	16/26 (61.5)	82/134 (61.2)
Stiffness of affected joint, n (%)	178/291 (61.2)	91/158 (57.6)	18/27 (66.7)	77/98 (78.6)
Antalgic positioning of affected joint, n (%)	83/284 (29.2)	42/153 (27.4)	8/26 (30.8)	53/87 (60.9)
Primary affected joint				
Hip	72/321 (22.4)	25/176 (14.2)	9/28 (32.1)	41/137 (29.9)
Knee	139/321 (43.3)	88/176 (50.0)	7/28 (25.0)	41/137 (29.9)
Ankle	36/321 (11.2)	18/176 (10.2)	5/28 (17.8)	22/137 (16.1)
Shoulder	27/321 (8.4)	18/176 (10.2)	4/28 (14.3)	8/137 (5.8)
Elbow	23/321 (7.2)	11/176 (6.2)	0/28 (0)	17/137 (12.4)
Wrist	17/321 (5.3)	12/176 (6.8)	1/28 (3.6)	2/137 (1.5)
Other	7/321 (2.2)	4/176 (2.3)	2/28 (7.1)	6/137 (4.4)
Monoarticular	312/321 (97.2)	175/176 (99.4)	27/28 (96.4)	129/137 (94.2)
Biarticular	9/321 (2.8)	1/176 (0.6)	1/28 (3.6)	5/137 (3.6)
Polyarticular	0/321 (0)	0/176 (0)	0/28 (0)	3/137 (2.2)
Laboratory investigations				
Leucocytes (cells/μL), median (IQR)	12,120 (9550 – 15,300) (283/321)	12,800 (10,140-15,930) (160/176)	9450 (7,980-11,870) (22/28)	17,500 (11,300 – 22,600) (125/137)
CRP (mg/L), median (IQR)	40.0 (18.0 – 61.0) (305/321)	36.0 (17.0-59.6) (168/176)	65.0 (25.0 – 129.0) (25/28)	107.5 (56.7 – 204.2) (134/137)
Positive hemoculture, n (%)	20/215 (9.3)	1/107 (0.9)	13/18 (72.2)	39/100 (39.0)
Known positive streptotest, n (%)	-	-	-	7/44 (15.9)
Radiologic investigation				
Effusion on ultrasound, n (%)	241/285 (84.6)	142/158 (89.9)	16/21 (76.2)	107/119 (89.9)
Preoperative osteolysis on x-ray, n (%)	22/289 (7.6)	11/159 (6.9)	6/27 (22.2)	8/94 (8.5)
Received MRI, n (%)	46/298 (15.4)	18/176 (10.2)	8/26 (30.8)	36/127 (28.3)
On antibiotic treatment at time of admission, n (%)	34/321 (10.6)	11/176 (6.2)	6/28 (21.4)	12/137 (8.8)
In septic shock on arrival, n (%)	0/321 (0)	0/176 (0)	0/28 (0)	2/137 (1.4)
Time since start of symptoms (days), median (IQR)	3 (2-5) (299/321)	2.5 (2-5) (160/176)	4 (3-7.75) (26/28)	2 (2-4) (105/137)
Infection type				
Uncomplicated arthritis	292/321 (91.0)	164/176 (93.2)	16/28 (57.2)	119/137 (86.9)
Arthritis with associated osteomyelitis/abscess	29/321 (9.0)	12/176 (6.8)	12/28 (42.8)	18/137 (13.1)
Post-operative period				
Events during post-operative hospital stay				
Reintervention, n (%)	21/321 (6.5)	6/176 (3.4)	9/28 (32.1)	49/137 (35.8)
ICU stay, n (%)	0/321 (0)	0/176 (0)	0/28 (0)	6/137 (4.4)
Total length of hospital stay, median (IQR)	5 (4-5) (321/321)	5 (4-5) (176/176)	8 (5.8-11.3) (28/28)	9 (6-12.5) (79/137)
Laboratory investigations 7 days post-discharge				
Leucocytes (cells/mL), median (IQR)	8,000 (6,258-9,375) (98/321)	7,700 (6,350-10,240) (43/176)	7000 (5,750-8500) (4/28)	7900 (6,000-9575) (44/137)
Leucocyte count within normal range, n (%)CRP (mg/L), median (IQR)	241/241 (100)	130/130 (100)	18/18 (100)	42/44 (95.5)
CRP (mg/L), median (IQR)	1.0 (0-2.0) (257/321)	0.4 (0-1.0) (140/176)	2.0 (0-16.0) (19/28)	3.6 (1.0-6.1) (47/137)
Sequelae	25/233 (10.7)	8/120 (6.7)	10/24 (41.7)	25/101 (24.8)
Osteolytic lesions, n (%)	23/233 (9.9)	8/120 (6.7)	9/24 (37.5)	21/101 (20.8)
Complete destruction of joint, n (%)	1/23 (4.3)	0/8 (0)	0/9 (0)	3/21 (14.3)
Epiphysiodesis, n (%)	5/233 (2.1)	1/120 (0.8)	3/24 (12.5)	2/101 (2.0)
Persistent stiffness, n (%)	0/233 (0)	0/120 (0)	0/24 (0)	1/101 (1.0)
Soft tissue destruction, n (%)	0/233 (0)	0/120 (0)	0/24 (0)	2/101 (2.0)

Number of patients included per variable differs based on availability of data for that specific variable

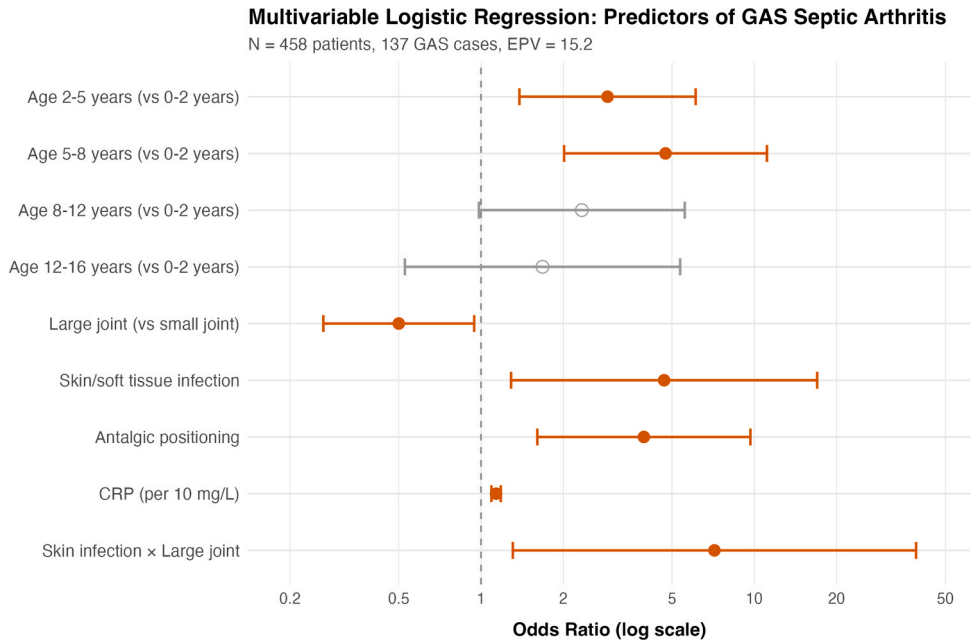

Fig. 2. Predictors of GAS Septic Arthritis. The Pseudo R^2 was 0.386 (range: 0.333–0.434) and the C-statistic was 0.890 (range: 0.869–0.908) confirming a good model fit and discrimination. The Hosmer-Lemeshow test was $\chi^2 = 13.05$ (P = 0.110) showing an appropriate level of model calibration. All VIF were smaller than 5, confirming absence of significant collinearity between variables.

Table 4
Multivariable risk model identifying clinical and demographic variables associated with Group A Streptococcal Septic Arthritis.

	Multivariable model	
Variable	OR (95% CI)	p-value
Age at time of admission (0-2 years is reference)	2.90 (1.38-6.10)	0.005
2-5 years	4.73 (2.01-11.12)	< 0.001
5-8 years	2.34 (0.98-5.56)	0.05
8-12 years	1.68 (0.53-5.35)	0.38
12-16 years		
Skin/soft tissues infection	4.68 (1.29-16.98)	0.02
Skin/soft tissue infection*joint type (Small joint is reference)		
Large joint	7.15 (1.31-39.06)	0.02
Antalgic positioning of affected joint	3.94 (1.61-9.67)	0.004
Primary affected joint is a large joint (small joint is reference)	0.50 (0.26-0.94)	0.03
CRP (per 10 mg/L)	1.14 (1.09-1.18)	<0.001

causative organism: aged 2–5 years (OR 2.90, 95% CI 1.38–6.10, p=0.005) or 5–8 years (OR 4.73, 95% CI 2.01–11.12, p<0.001), presenting with antalgic positioning of the joint (OR 3.94, 95% CI 1.61–9.67, p=0.004), and having an increased CRP (OR 1.14 per 10 mg/L increment, 95% CI 1.09–1.18, p<0.001). Presenting with a SA in a large joint decreases the risk of GAS being the causative organism (OR 0.50, 95% CI 0.26–0.94, p=0.03). Presenting with a skin/soft tissue infection also increases the risk of GAS but the increased risk depends on the size of affected joint: the risk increases in a child with a skin/soft tissue infection and a small, affected joint (OR 4.68, 95% CI 1.29–16.98, p=0.02), but increases even further in a child with a skin/soft tissue infection and a large, affected joint (interaction OR 7.15, 95% CI 1.31–39.06, p=0.02).

The second multivariable risk model (Fig. 3, Table 5) shows that in children with SA, the following variables increase the risk of developing sequelae: presenting with a concomitant skin/soft tissue infection (OR 3.80, 95% CI 1.46–9.88, p=0.006), being on pre-hospital antibiotics (OR 2.37, 95% CI 1.29–4.33, p=0.005), longer symptom duration (OR 1.08 per day, 95% CI 1.03–1.12, p<0.001), having a complicated infection with osteomyelitis (OR 4.47, 95% CI 2.16–9.27, p<0.001), and requiring a reintervention (OR 3.64, 95% CI 1.79–7.42, p<0.001). Preoperative osteolysis on x-ray showed a trend toward increased sequelae risk but did not reach statistical significance (OR 3.17, 95% CI 0.90–11.15, p=0.07). The risk of sequelae increases with increasing orthopaedic symptom duration (Fig. 4). S. aureus has the highest risk of sequelae regardless of symptom duration, with GAS infections only slightly lower. Sequelae risk was further influenced by other clinical variables (Table 5), discussed above.

Discussion

In this exploratory study, we found a significant increase in the incidence of GAS SA in 0–4-year-olds and 5–9-year-olds between 2010 and 2023. GAS SA is independently associated with children aged 2–8 years, presenting with a concomitant skin infection, a small affected joint, an antalgic position and an elevated CRP. However, in patients with a concomitant skin infection, large joints are more strongly associated with GAS SA. SA sequelae are clinically associated with GAS or S. aureus infections, presenting with a concomitant skin infection, having received pre-hospital antibiotics, having a complicated SA, and having a longer orthopedic symptom duration. Our results suggest that GAS is emerging as a pathogen of interest in pediatric osteoarticular infections with a similar baseline sequelae risk profile as S. aureus SA, but a distinct clinical presentation at admission from non-GAS SA.

An increase in iGAS infections has been noted globally since the 2010s [6,21], however, to date, this is the first study to document the changing epidemiology of GAS SA, as a specific subtype of iGAS. Lenglart et al. estimated the increase in pediatric osteoarticular GAS infections across 15 European countries [6], including France, at 62.7% (95% CI −8.3–157.9) between 2018 and 2024. This is lower than the 97.4% (95% CI 25.6–210.1) increase (Table 2) we found in our cohort. A potential explanation for this difference is that we only included SA, while Lenglart and colleagues included all types of osteoarticular infections. As surgical debridement and obtaining bone cultures are only recommended after initial failure of medical treatment for osteomyelitis [22], some of the GAS osteomyelitis may remain unidentified, leading to an underestimation of the increased incidence. However, Lenglart et al.

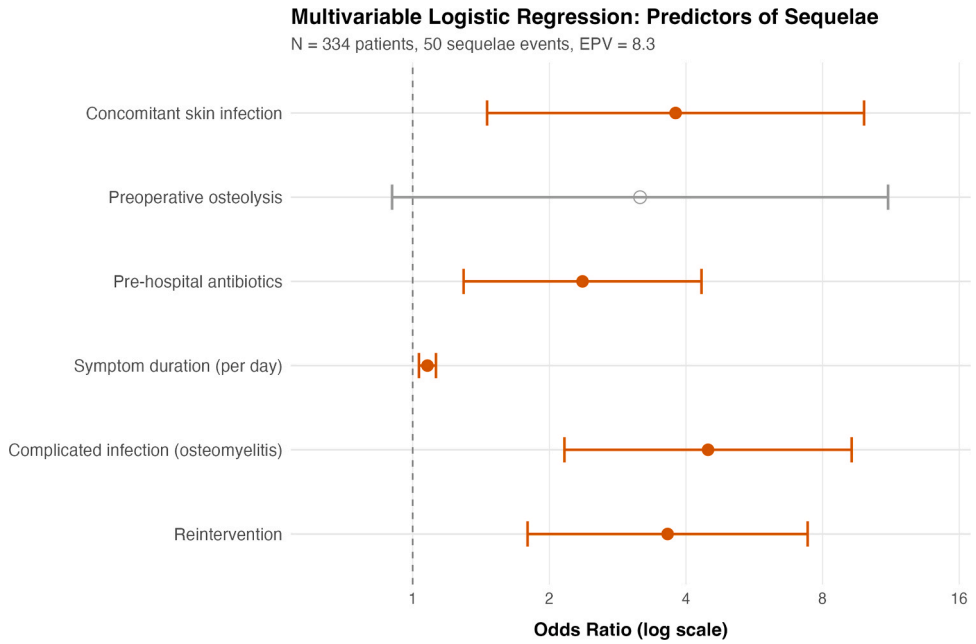

Fig. 3. Predictors of Sequelae. The Pseudo R^2 was 0.262 (range: 0.242–0.289) and the C-statistic was 0.851 (range: 0.840–0.861) confirming a good model fit and discrimination. The Hosmer-Lemeshow test was $\chi^2 = 5.62$ (P = 0.585) showing a good level of model calibration. All VIF were smaller than 5, confirming absence of significant collinearity between variables. The sensitivity analysis incorporating causative organism showed that the results are robust to adjustment by organism (Table 4, Table S8). We observed only minor improvements in discrimination (C-statistic 0.862, 0.012 increase) and model fit (pseudo R^2 0.286, 0.024 increase), without multicollinearity (all VIF <5) and maintained good calibration ($\chi^2 = 8.18$, p = 0.416) in the sensitivity analysis model.

Table 5
Multivariable analysis of variables associated with a sequelae.

	Multivariable risk model		Multivariable risk model sensitivity analysis	
Variable	OR (95% CI)	p-value	OR (95% CI)	p-value
Skin/soft tissues infection	3.80 (1.46-9.88)	0.006	2.74 (1.22-6.11)	0.010
Pre-operative osteolysis	3.17 (0.90-11.15)	0.070	2.81 (0.73-10.83)	0.130
On antibiotic treatment at time of admission	2.37 (1.29-4.33)	0.005	2.31 (1.20-4.41)	0.010
Time since start of symptoms (days)	1.08 (1.03-1.12)	<0.001	1.09 (1.05-1.14)	<0.001
Infection type (uncomplicated arthritis is reference)	4.47 (2.16-9.27)	<0.001	3.63 (1.71-7.72)	<0.001
Reintervention	3.64 (1.79-7.42)	<0.001	2.38 (1.09-5.23)	0.030
Germ type				
Group A Streptococcus (reference)	-			
Kingella Kingae			0.33 (0.14-0.77)	0.010
Staphylococcus aureus			1.36 (0.71-2.60)	0.350
Other/unknown			0.42 (0.17-1.01)	0.050

also show significant inter-country differences in incidence evolution between 2018 and 2024, according to them due to differing stay-at-home orders and subsequent changes in population-level immunity. Fig. 1 clearly shows a slowing down of the incidence increase in France, during COVID-19, with a catch-up of cases post-COVID.

Mortality rates from pediatric iGAS are estimated at 3.6–5%, while pediatric intensive care (PICU) admission rates are estimated between 16.3–27.7% across Europe. [1,4–7] Only one study reported on PICU admissions and death per subgroup of iGAS, with Cardoso et al. reporting 8 PICU admissions (5.9%) and 1 death (0.7%) among 135 musculoskeletal iGAS infections across Europe. [7] We didn't register a single death in our cohort and only registered an ICU admissions rate of 4.4%, which confirms the number from Cardoso et al. These numbers seem to suggest that musculoskeletal iGAS is among the less aggressive forms of iGAS with less evolution to a fulminant and disseminated disease. Further research is needed to understand if this less aggressive clinical presentation might be driven by different GAS *emm*-type [23] with a preference for musculoskeletal tissue [24], or if other clinical or treatment factors are at play that help contain the disease.

Our multivariable GAS risk model identified an elevated CRP and antalgic positioning of the joint, aligning with two of the four Kocher-Caird criteria, as independent predictors of GAS SA. Unlike the Kocher-Caird criteria, we were unable to identify a clear CRP-cut-off above which GAS becomes the most likely pathogen due to the small number of S. aureus SA in our study. The "elevated CRP" in this context should be interpreted as the higher the CRP, the higher the likelihood of a GAS SA, without an absolute risk assessment available based on this current study. Nevertheless, this finding confirms that tools developed to distinguish SA from transient synovitis may also carry discriminatory value across causative organisms, especially when differentiating between K. kingae and non-K. kingae SA [25]. The model further confirmed that GAS SA is independently associated with small joint infections compared to other causative organisms, consistent with prior case reports. [15,26] However, in the subgroup of patients with a concomitant skin infection, the association is more strongly associated with large joints instead. Due to limited power and several skin infections grouped together in the "concomitant skin infection" variable, clinical implications of this finding could not be assessed further or be meaningfully interpreted in this study. Regarding predisposing or concurrent infections, 33% of GAS SA patients had a concurrent skin

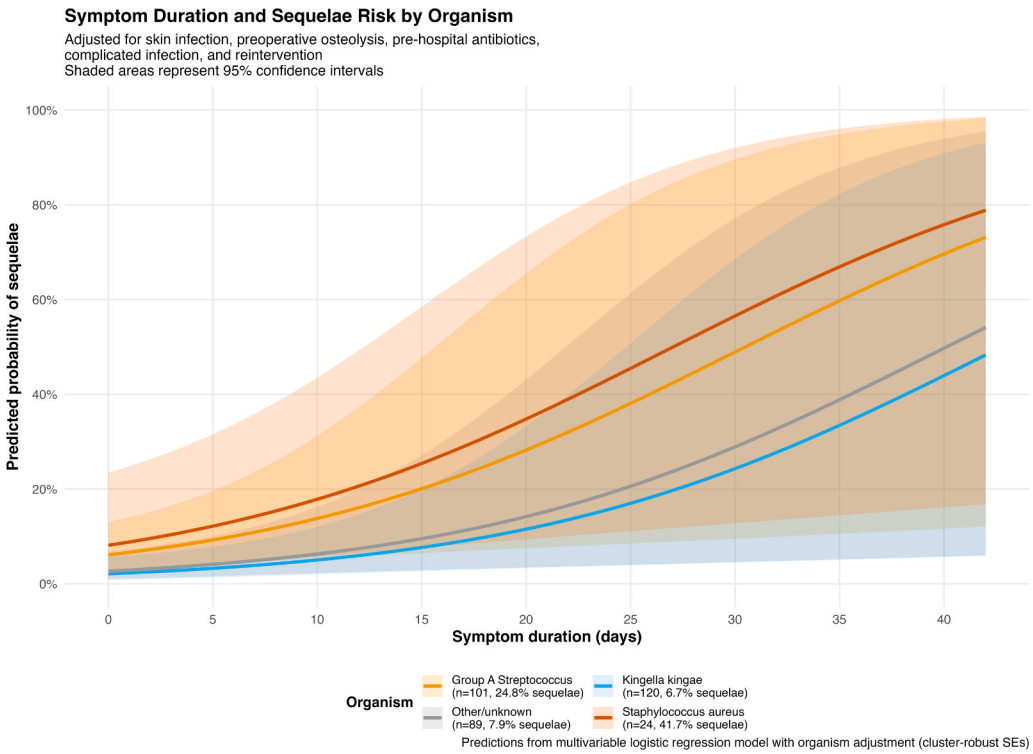

Fig. 4. Symptom duration and sequelae risk by organism.

infection, of which 81% were varicella, aligning with the well-established association between varicella and iGAS. [4,6] However, only 4% had a prior influenza infection and no prior RSV cases were identified, contrasting with the recent study by Lenglart et al., where both viruses are recognized triggers. [6] This may suggest that viral predisposition to iGAS is not uniform, and that certain viruses, such as varicella, are more specifically linked to musculoskeletal manifestations than respiratory viruses such as influenza or RSV. Taken together, these findings suggest that the clinical signs of GAS SA represent a convergence of established risk factors from both the SA and iGAS literature. Combined with GAS SA-specific features such as the characteristic age range and preference for small joints, this is a profile that both orthopedic surgeons, primary care providers and pediatricians should recognize to ensure prompt identification and treatment.

Our sequelae risk model had insufficient power to identify specific variables associated with sequelae in GAS patients alone (Table S9) or compared to S. aureus patients, clinically the most relevant questions, given the high rate of sequelae in both groups (Table 3). Nevertheless, our model was able to identify delayed treatment, presence of osteomyelitis, pre-hospital antibiotics, and the need for reintervention as independent predictors of sequelae, across causative organisms. Delayed treatment is known as an independent predictor for sequelae, as well as a predictor for the development of osteomyelitis, and an increased intervention rate. [27–29] However, presence of osteomyelitis and an increased intervention rate as independent predictors were not previously identified as independent predictors in the pediatric SA literature. It is unclear what the role of pre-hospital antibiotics is in the process of developing sequelae. It may be an indicator of delayed treatment, or more severe disease requiring urgent antibiotic treatment. However, given that it is independently associated with sequelae, there may be another, currently poorly understood, process at the basis of this phenomenon, that merits further exploration in future studies. The presence of skin and soft tissue infections as a concomitant infection requires further validation in other studies, to clarify if this is a variable associated with sequelae across all causative pathogens, or specifically in GAS SA. With a 24% sequelae rate in our cohort, and a reconfirmation that delayed treatment is an important predictor of sequelae, the clinical take-home message for clinicians treating SA is that time is of the essence in patients where GAS is suspected. The value of additional diagnostic tests should be balanced against the delay to treatment they may cause.

This study has several limitations. First, its retrospective design introduces the risk of incomplete data extraction and misclassification of variables across participating institutions. Second, while complete case ascertainment was pursued across all 26 tertiary pediatric orthopedic departments in mainland France, our control group was drawn from a single Parisian tertiary center. Internal validation suggested that the Necker GAS SA population may be more affluent and present with clinically more severe disease than the broader French SA population, which, if equally present in non-GAS controls, may lead to an underestimation of the odds ratios in our multivariable models and limit the external validity of the findings. Additionally, because of the difference in affluence and urbanization between cases and controls, we are unable to interpret these demographic variables in our study, despite the fact that our data suggests there may be a correlation between socioeconomics and outcomes. Third, as GAS SA is a rare disease, our sample size was insufficient to power a sequelae analysis specific to GAS SA patients, which was clinically the most relevant question. Fourth, *emm*-typing data were only available for institutions where typing is performed as standard practice, limiting our ability to draw conclusions about the relationship between GAS *emm*-type and clinical presentation or outcomes. Fifth, this study aimed to build as much as possible on existing orthopaedic and infectious disease literature to inform models, however, this study remains of an exploratory nature, which may lead to identifying association based on coincidence rather than a true biological relationship.

In conclusion, this study documents a significant and ongoing increase in GAS SA in young children in France, consistent with the global rise in iGAS. GAS SA presents with a distinct clinical profile drawing on features from both the SA and iGAS literature and presents a sequelae rate comparable to S. aureus SA. Delayed treatment remains a critical and modifiable predictor of poor outcomes, making early recognition by

orthopedic surgeons, pediatricians, and primary care providers essential. Future multicenter studies with greater statistical power are needed to confirm the clinical profile of GAS SA patients and better characterize sequelae risk within the GAS SA population specifically.

CRediT authorship contribution statement

Conceptualization: MP, EH; Data curation: MP, EH; Formal analysis: MP; Investigation: MP, EH, JBL, AB, GAS-Ortho author group; Methodology: MP, EH; Project administration: EH; Resources: AB; Software: MP; Supervision: MP, EH, PRS; Validation: MP; Visualization: MP; Writing - original draft: MP; Writing - review and editing: everyone. All authors reviewed and approved the final version of the manuscript.

Ethics declaration

The authors have NOT obtained informed consent from participants or their legal representatives. France does not require patient consent for retrospective, observational studies solely using de-identified data from medical records.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was approved by the Comité de Protection des Personnes Sud Méditerranée I. (Approval No. #00011928)

Declaration of Generative AI and AI-assisted technologies in the writing process

No generative AI was used in the preparation of this manuscript.

Funding

None.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Antoine Josse:** Honoraria for educational activities from Arthrex (€1999), Orthofix (€50), and Stryker (hospitality, €12); travel support from Implancast France (conference attendance, €316). **Nicolas Mainard:** Hospitality (meal, €16) provided by NORAKER. **Zagorka Pejin-Arroyo:** Consulting/advisory activities for Orthofix S.R.L. (2022–2024); honoraria from Orthofix S.R.L. for educational activities, lectures and expert presentations; travel and meeting support from Orthofix SA/ Orthofix S.R.L. (2022–2024).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2026.106847.

Data Availability

An aggregated anonymized dataset is available upon reasonable request from the corresponding author. Individual-level data will not be shared, to protect the privacy of the minors involved in this study.

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